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Polypharmacy among Older Individuals with COPD: Trends between 2000 and 2015 in Quebec, Canada

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ABSTRACT

The treatment of chronic obstructive pulmonary disease (COPD) and concomitant diseases requires several medications. Yet there is little data on how the pharmacological burden progressed over time among older individuals with COPD. We aimed to: 1) describe the proportion of older adults with COPD in Quebec, Canada, that were exposed to polypharmacy (≥10, ≥15 or ≥20 medications/year) between 2000 and 2015; 2) calculate the proportion of individuals receiving specific prescriptions for COPD during this period. We conducted a population-based cohort study with the Quebec Integrated Chronic Disease Surveillance System. Individuals aged ≥66 years with COPD and covered by the universal public drug plan were included. We calculated the total number of drugs used at least once by each individual during each of the studied years, and used age-standardized proportions to compare proportions of users between the years. The average number of drugs used increased from 12.0 in 2000 to 14.8 in 2015. The proportion of individuals exposed to polypharmacy increased (≥10 drugs: 62.0% to 74.6%;≥15 drugs: 31.2% to 45.4%; ≥20 drugs: 12.3% to 22.4%). The proportion of individuals receiving long-acting bronchodilators increased from 18.7% in 2000 to 69.6% in 2015. The use of short-acting bronchodilators decreased from 81.5% to 67.9%, and that of inhaled corticosteroids from 60.6% to 26.0%. The proportion of users of methylxanthines decreased from 15.0% to 1.9%. Older individuals with COPD are increasingly exposed to polypharmacy. Identifying which polypharmacy is beneficial is a priority.

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COPD; COPD treatment; polypharmacy; elderly

Introduction

Chronic obstructive pulmonary disease (COPD) affects around 15% of the population over 65 years of age (1). COPD is associated with increased health care use and poor quality of life (2). Fortunately, a variety of medications are now available to improve lung function and reduce complications, including exacerbations (3).

Older individuals with COPD also present numerous co-morbidities (4,5), which increases the probability of using several medications, known as polypharmacy. Such complex medication regimens have substantial impact on compliance, side effects, and drug-drug and drug-disease interactions (4,6). Yet the pharmacological burden that COPD individuals have been facing in the last decade is not well defined. We therefore aimed at reporting the prevalence of polypharmacy and illustrating the particular trends of COPD-related medication use among older patients with COPD in the province of Quebec, Canada, between 2000 and 2015.

Methods

Data source and population

We used the Quebec Chronic Disease Surveillance System (QICDSS). This database is composed of five health administrative databases grouping data about physician services fees, pharmaceutical services, hospitalization data (Med-Echo), registration plan, and death registry. The pharmaceutical database provides information on drugs dispensed, including drug names, dispensing dates, and number of days' supply. Around 90% of the older population in Quebec is covered by the public drug plan (7). The QICDSS permits the identification of chronic diseases with validated algorithms (7) and the calculation of a co-morbidity score (8).

COPD definition

We used a validated definition of COPD (9) to identify individuals with the disease. The International classification of diseases (ICD) 9th revision codes 491–492 and 496, and the ICD-10-CA codes J41-44 were used to ascertain cases. To be included, an individual had to have two diagnosis of COPD in the physician database in a two year-period or one primary or secondary diagnosis in the hospital database. There was no restriction on age as the population included only individuals 66 years and older. We did not apply further inclusion or exclusion criteria to the definition (such as smoking patterns, which are not available in the database, or the presence of other respiratory conditions). This definition

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has a sensitivity of 85% (95%CI: 77.0–91.0) and a specificity of 78.4% (95% CI: 73.6–82.7) (9) and is notably used by public health authorities to estimate the burden of COPD (7,10,11). Nonetheless, in order to increase the positive predictive value, we restricted our analysis to individuals who had used a medication specific to COPD in the year before or in the year studied.

We included individuals based on their fulfilment of COPD definition every fiscal year, from 2000 to 2015 (Fiscal year begins April 1st and ends March 31st). An individual can therefore meet the case definition criteria a year, but not be included the following year. This allowed us to further reduce the number of false positive cases over the years. Individuals also had to be alive and covered by the universal public drug plan throughout the studied year to assess the total number of medications used during this time period.

Polypharmacy and medication use

We defined polypharmacy as the yearly use of at least 10 different medications (12). We also conducted analysis using thresholds of 15 and 20 medications. We compiled the number of medications prescribed to each individual through a fiscal year by using the common denominations (chemical name) of the drugs. We assessed whether or not individuals used the following COPD-related medications, as defined by at least one billing in the studied year: long-acting bronchodilators, short-acting bronchodilators, inhaled corticosteroids, oral corticosteroids, methylxanthines, roflumilast, antibiotics and smoking cessation medications. Chronic and acute use of medications were not differentiated, as we only evaluated the presence of at least one claim of the respective medications through the year studied.

Statistical analysis

We calculated the mean number of medications used by each individual each year. We also calculated the proportion of individuals exposed to at least 10 different medications through the year, at least 15 or at least 20 as well as the proportion of those using the COPD related medications. In order to make comparisons, we calculated age-and sex-standardized proportions according to the 2001 Quebec population. *T*-tests were used to compare continuous variables and we tested trends, adjusted for sex and age, using Poisson regression models with robust error variance estimator. All analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

Ethics

The use of the QICDSS has been approved by the custodians of the databases, the provincial Public Health Research Ethics Board and the Quebec Commission protecting access to information.

Results

The number of included individuals varied from 68,532 in 2000 to 117,005 in 2015 (Table 1). Over the years, the population comprised an increasing number of women, older individuals, and individuals with more co-morbidities.

The mean yearly number of medications increased from 12.0 in 2000 to 14.8 in 2015 ($p < 0.0001$) (not shown). Polypharmacy simultaneously increased during the period (Table 1, Figure 1). From 2000 to 2015, the proportion of individuals using $\geq$10 medications per year increased by 12.6% (from 62.0% to 74.6%) with a relative increase of 1.3% per year ([95% confidence interval (CI):1.2;1.4], $p < 0.0001$); $\geq$15 medications, by 14.2% (from 31.2% to 45.4%) with a relative yearly increase of 2.7% ([CI:2.6;2.8], $p < 0.0001$) and $\geq$20 medications, by 10.1% (from 12.3% to 22.4%) with a relative yearly increase of 4.3% ([CI:4.1;4.4], $p < 0.0001$).

Patterns of COPD-related medication use over time differed according to the medications (Table 1, Figure 2). The proportion of long-acting bronchodilators users increased over the years (18.7%–69.6%), with a relative increase of 7.0% per year ([CI:6.9;7.1], $p < 0.0001$), whereas the proportion of short-acting bronchodilators users decreased (81.5%–67.9%), with a relative decrease of 1.2% per year ([CI:1.1;1.2], $p < 0.0001$). Inhaled corticosteroids were common in early years (60.6%) but their use decreased drastically to reach 26% in 2015; translating in a relative decrease of 5.9% per year ([CI:6.0;5.8], $p < 0.0001$). On the other hand, oral corticosteroids, antibiotics and smoking cessation medications remained fairly stable. The use of methylxanthine decreased over the years, whereas the use of roflumilast slightly increased after its marketing date before reaching a low, but stable, level.

Discussion

Our results show how polypharmacy is common among older people with COPD and is steadily increasing between 2000 and 2015.

Other studies have suggested high rates of polypharmacy among older COPD patients. In the UK, Hanlon et al. indicated that 52.0% of their cohort of community-dwelling adults (median age: 62 years) received >5 medications (4). In Italy, the proportion was 59.5% among the 22,505 patients (64% $\geq$65 years old) in primary care (13). Our results contrast with the proportion of individuals exposed to polypharmacy in the general population. In Canada, 27% of adults older than 65 years received at least 10 different medication classes in 2014 (12), while it was 75% among our COPD population. To our knowledge, this is the first study to portray a population-based evaluation of medication use over fifteen years among COPD patients. It allows for the visualization of the increase of medications and is a first step towards the objective of rationalizing medication use among older patients with COPD to find the best risk to benefit ratio.

The increase in the total number of medications has consequences. Together with increasing management

Table 1. Characteristics of the Older Adults with COPD in Quebec, Canada, and their Use of Medication between 2000 and 2015.

	2000		2005		2010		2015	
	N = 68,532		*N* = 83,927		*N* = 97,682		*N* = 117,005	
Characteristics	*N*	%	*N*	%	*N*	%	*N*	%
Age (mean ± SD)	76.3 ± 6.3		77.1 ± 6.6		77.3 ± 6.9		77.2 ± 7.2	
66–75	34,030	49.7	37,233	44.4	43,251	44.3	54,865	46.9
76–85	28,110	41.0	36,946	44.0	41,062	42.0	44,615	38.1
86+	6,392	9.3	9,748	11.6	13,369	13.7	17,525	15.0
Sex								
Female	32,922	48.0	43,377	51.7	52,514	53.8	64,326	55.0
Male	35,610	52.0	40,550	48.3	45,168	46.2	52,679	45.0
Co-morbidity (mean ± SD)	3.0 ± 2.3		3.3 ± 2.5		3.4 ± 2.6		3.5 ± 2.7	
Asthma	23,347	34.1	35,072	41.8	41,941	42.9	50,009	42.7
Diabetes	13,068	19.1	21,249	25.3	29,602	30.3	37,954	32.4
Heart failure	14,137	20.6	18,820	22.4	21,118	21.6	24,605	21.0
Hypertension	37,327	54.5	58,516	69.7	73,661	75.4	89,681	76.6
Osteoporosis	9,824	14.3	20,306	24.2	29,383	30.1	38,781	33.1
Co-morbidity score [8][b]								
0	14,381	21.0	25,090	29.9	32,587	33.4	44,574	38.1
1	909	1.3	1,614	1.9	24,179	24.8	23,983	20.5
2–3	30,375	44.3	31,020	37.0	16,381	16.8	19,018	16.3
4–5	12,161	17.8	13,205	15.7	11,543	11.8	13,204	11.3
6+	10,706	15.6	12,998	15.5	12,992	13.3	16,226	13.9
GP visits (mean ± SD)	0.2 ± 1.0		0.9 ± 2.4		3.0 ± 3.6		3.2 ± 3.4	
Hospitalizations (mean ± SD)	0.5 ± 1.0		0.5 ± 0.9		0.4 ± 0.9		0.4 ± 0.9	
Medications								
Long-acting bronchodilators	12,857	18.7[a]	32,705	39.0[a]	63,718	64.6[a]	81,895	69.6[a]
Long-acting beta-agonists	12.857	18.7[a]	30,242	36.1[a]	49,226	50.2[a]	65,491	55.8[a]
Long-acting anticholinergics	0	NA	9,868	11.8[a]	45,546	45.7[a]	47,989	40.5[a]
Short-acting bronchodilators	56,121	81.5[a]	65,430	77.8[a]	69,464	71.3[a]	79,159	67.9[a]
Inhaled corticosteroids	41,383	60.6[a]	40,185	48.0[a]	30,692	31.8[a]	29,976	26.0[a]
Oral corticosteroids	18,696	27.3[a]	22,248	26.8[a]	27,253	28.2[a]	33,800	29.2[a]
Methylxantines	10,266	15.0[a]	5,799	6.9[a]	3,718	3.8[a]	2,213	1.9[a]
Roflumilast	0	NA	0	NA	0	0[a]	284	0.2[a]
Antibiotics	38,915	57.3[a]	83,927	49.6[a]	51,686	53.3[a]	60,952	52.2[a]
Smoking cessation treatments	2,569	4.5[a]	3,221	4.8[a]	5,060	6.4[a]	6,198	6.3[a]
Yearly number of medications								
10–14	21,276	30.9[a]	26,642	31.5[a]	29,913	30.4[a]	34,391	29.2[a]
15–19	12,809	18.9[a]	17,769	20.9[a]	23,227	23.1[a]	27,704	23.0[a]
20+	8,106	12.3[a]	13,193	15.8[a]	19,868	20.2[a]	26,713	22.4[a]

[a]Denotes age and sex-standardized proportions according to 2001 Quebec population. Due to the population-based nature of the data, no confidence intervals are presented to facilitate reading. Confidence intervals are available on request.
[b]Combined Co-morbidity Index of Charlson and Elixhauser [8].
NA: Long-acting anticholinergics were reimbursed from 2002/2003; roflumilast was introduced in 2011 in Canada but is only reimbursed by the public drug plan under specific circumstances which limits its use.

complexity, it leads to possible drug–disease and drug–drug interactions and more side effects (6,14). Because of pharmacodynamic and pharmacokinetics changes associated with aging (15), older people are more susceptible to such adverse events. Iatrogenic risk associated with polypharmacy is thus a genuine concern for older adults with COPD. The growing trends we have identified in our study raise questions about the safety of these therapies. In fact, polypharmacy is a complex phenomenon, involving a wide variety of medication combinations, which has not yet been fully described and understood (16). Nevertheless, it has been associated with myriad negative outcomes in older populations, such as hospitalizations, falls or frailty (17–20). Quality may be at stake: one in ten older COPD patients could receive potentially inappropriate medications (21), while clinical guidelines are not always followed (22). To ensure optimal pharmacotherapy, there may be a necessity to identify what medications provide the greatest benefits, the lowest risks and the better quality of life. Finding such optimal therapy may prove difficult (23) and should involve the patient.

Pharmacological management of co-morbidities may lead to significant medication burden for older adults with COPD. The study population had an average of three concomitant diseases. Although the number of co-morbidities varies considerably between studies (24), multimorbidity is a constant concern. In a group of 826 patients with COPD in Turkey, 84.5% had at least one co-morbidity (25). In another study involving 1,659 patients in the United States and Spain, the average number of co-morbidities was 6 (SD:3.5, range 0–21) (26). The greater presence of co-morbidities in this last study can be explained by the difference in population (patients were recruited in pulmonary clinics) and by the methodology (co-morbidities were recorded from direct questioning and review of medical records).

With such multimorbidity, optimizing pharmacological treatment reveals challenging in older adults and oldest old individuals with COPD (27). In addition, they often have a limited functional reserve and frailty that will also affect treatment choices (27). In order to improve physical functioning with medications, it is necessary to carry out a holistic evaluation, taking into account the patient's cognitive

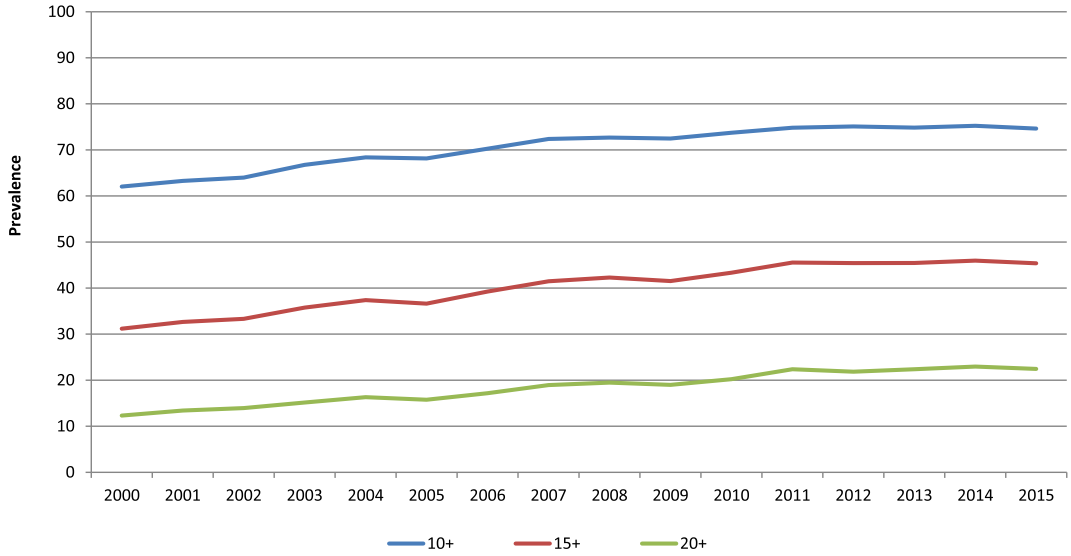

Figure 1. Age- and sex-standardized proportions of older adults with COPD in Quebec, Canada, exposed to three levels of polypharmacy, between 2000 and 2015.

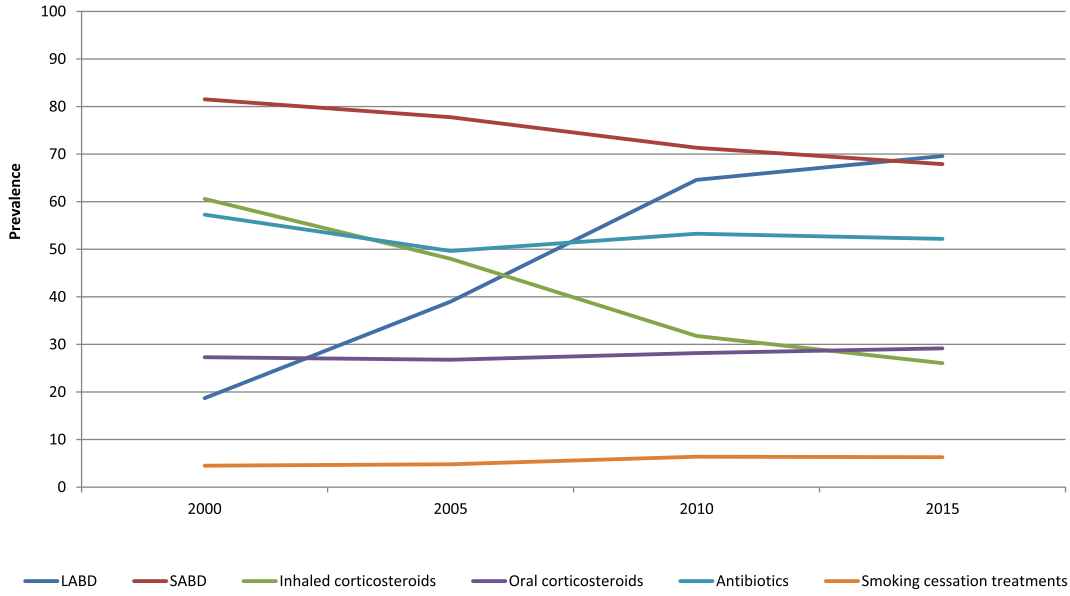

Figure 2. The use of COPD medications by older adults with COPD in Quebec, Canada, between 2000 and 2015. *LABD: Long-acting bronchodilators; SABD: Short-acting bronchodilators

and functional status and co-morbidities together with their willingness to be treated. If polypharmacy proves inevitable for many patients, it may be necessary to make rational choices and prioritize certain medications. Indeed, the escalation in medication use that we have described over the years is unlikely to be sustainable, either from the perspective of the individual or of society.

Our study showed different trends in COPD medication use. Such trends have been described elsewhere. In a population-based Danish study, the overall use of long-acting bronchodilators among adults increased between 2000 and 2016, while the use of inhaled corticosteroids (alone or fixed-dose combinations) remained relatively stable (28). According to the authors, the prompt acceptance of long-acting muscarinic antagonists as a new treatment for COPD drove the increase in the use of long-acting bronchodilators, which is likely analogous to the phenomenon we observed in our population. The authors also hypothesized that the stable use of inhaled corticosteroids among bronchodilators users in their study is in fact explained by a decline in the use of this therapy among COPD patients (since they could not differentiate indications for therapies). This concurs with the reduction in inhaled corticosteroids we observed, which itself is coherent with the increased awareness about safety issues of inhaled corticosteroids in this population (29,30), and with guidelines recommendations (31). Finally, similar to our findings, Kwak et al. found a low average prescription rate for smoking cessation therapies: between 2007 and 2012, 3.64% of their active smokers with COPD used these medications (32).

This study has limitations. First, the case definition suffers from limitations inherent to the use of administrative databases. Indeed, the presence of COPD could not be confirmed clinically because we did not have access to

spirometry results and it was not possible to do further tests with the study population. Some of the symptoms attributed to COPD may be due to alternative conditions such as asthma (33) and chronic heart failure (34), inducing a possible misclassification bias. The limited specificity of the case definition can therefore lead to a number of false positives. However, this case definition applied in the QICDSS revealed a prevalence of COPD consistent with other population-based data that included spirometry measures (10). Yet, the fact that the definition predominantly identifies moderate to severe COPD (10) coupled with the fact that we only included people who had recently used a COPD medication, may have resulted in the presence of a more severely affected population. This may have overestimated the number of individuals exposed to polypharmacy, but as the same criterion was applied over the years, the impact should be uniform in the study period. Second, only one claim was required to evaluate use of medications. Our definition of polypharmacy did not imply simultaneous use of medications, which may theoretically result in individuals using large number of medications through the year, but none at the same time. Nonetheless, we applied the same definition over the year and used population-based data that allowed us to perform trends. On the other hand, we have underestimated the medications COPD patients are exposed to because we did not include over the counter products as they are not reimbursed under the drug plan. Finally, we did not assess adherence to treatment. While it would have provided a more thorough portrait of the quality of medication use, this analysis was beyond the objectives of the study.

Conclusion

The proportion of older individuals with COPD using at least 10 medications per year increased gradually to reach nearly three quarters in 2015. There is a need to explore if this increase in medications translated into benefits for the patients and the healthcare system. In general, there is a need to fully apprehend medications used by these patients, in order to reduce the burden polypharmacy may generate and ensure patients fully benefit from pharmacotherapy.

Disclosure statement

No financial interest or benefit has arisen from the direct applications of our research.

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